γ-Lactam Analogues of Penicillanic and Carbapenicillanic Acids

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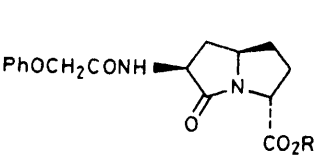
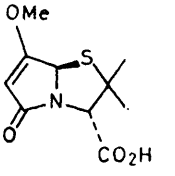
Synthesis and biological activity of γ-lactam analogues (**1**) and (**2**) of carbapenicillanic and penicillanic acid, respectively, are described.

The minimum structural features believed to be essential for antimicrobial activity in the β-lactam antibiotics have undergone considerable revision since the discoveries of thienamycin,[1] clavulanic acid,[2] nocardicin,[3] and more recently, the monobactams.[4] It now appears that the minimum structural requirement for biological activity is a suitably activated β-lactam ring. We decided to explore the possibility that biologically active compounds devoid of the β-lactam moiety could be obtained *via* synthesis, and have now prepared the fused γ-lactams (**1**) and (**2**). Although the synthesis of γ-lactam analogues of penicillin was reported[5] in 1949, the present work is the first synthesis of stereochemically well-defined γ-lactams related to the penicillins.

5-Methoxycarbonyl-1-pyrroline 1-oxide† (**3**), obtained from methyl nitroacetate and acrolein (Scheme 1), was allowed to react with methyl acrylate (CH_2Cl_2, 25 °C, 2 h) to afford an inseparable mixture of isoxazolidines (**4**) and (**5**). Reduction with Raney nickel (H_2, 1 atm, MeOH, 40 °C, 36 h) gave a mixture of amino-alcohols (**6**) and (**7**). Refluxing

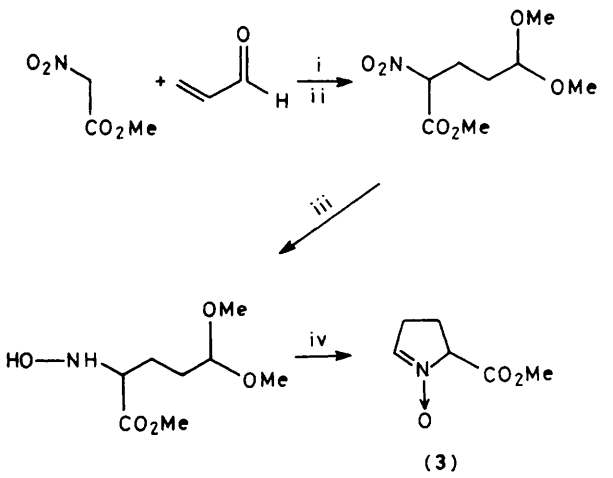


(**1**) **a**; R = Me
b; R = K



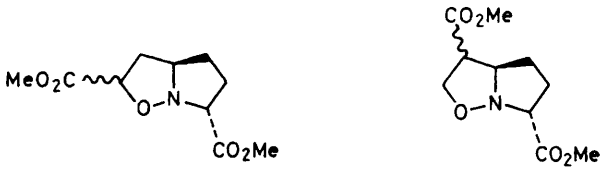
(**2**)

† All new compounds gave satisfactory spectroscopic and analytical data.



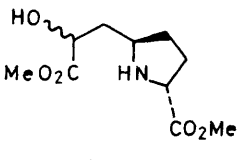
(3)

Scheme 1. i, NaOMe, MeOH, −40 °C, 3 h; ii, HCl (g), −40 to 25 °C; iii, Al–Hg, H_2O, Et_2O; iv, 1 M HCl (aq.), 25 °C, 2 h.

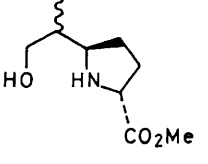


(4)

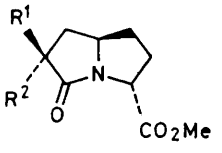
(5)



(6)



(7)



(8a) R^1 = H, R^2 = OH

(8b) R^1 = OH, R^2 = H

(9a) R^1 = H, R^2 = *p*-$MeC_6H_4SO_3$

(9b) R^1 = *p*-$MeC_6H_4SO_3$, R^2 = H

(10) R^1, R^2 = O

(11) R^1 = N_3, R^2 = H

this mixture in methanol (1 h) effected cyclisation of regioisomer (**6**) to the desired γ-lactam (**8**), which was separated from the crude reaction mixture by flash chromatography on silica gel (EtOAc), in an overall yield of 14% from (**3**). ^{1}H N.m.r. spectroscopy showed this to be a mixture of the 7α- [m.p. 114—115 °C, ν_{max} ($CHCl_3$) 3380, 1745, and 1700 cm^{-1}] and 7β- [m.p. 104—106 °C, ν_{max} ($CHCl_3$) 3360, 1742, and 1690 cm^{-1}] isomers (**8a**) and (**8b**), respectively, in a ratio of 85:15. Pure samples of each were obtained by chromatography and the stereochemistry of the minor isomer

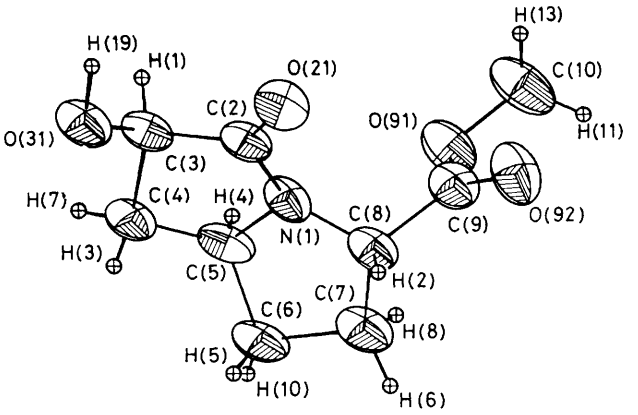


Figure 1

was unequivocally established by *X*-ray crystallography (Figure 1).

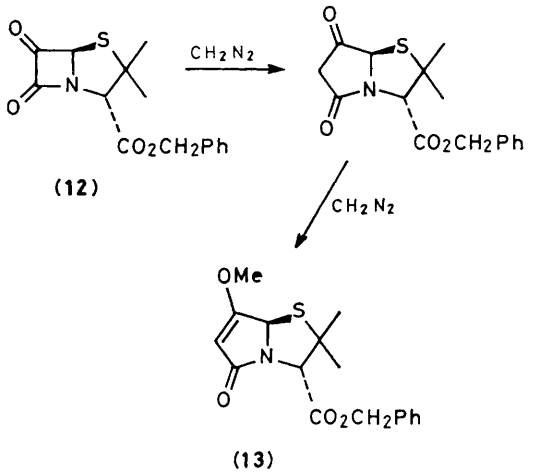
Crystal data: $C_9H_{13}NO_4$, M = 199.21, triclinic, space group $P\bar{1}$, a = 6.637(4), b = 7.072(2), c = 11.377(4) Å, α = 77.60(3), β = 70.83(4), γ = 76.52(4)°, U = 484.9 Å^3, Z = 2, D_m = 1.36 g cm^{-3}. 1241 Independent reflections were measured by four circle (CAD-4) diffractometry using Mo-K_α radiation (λ = 0.71069 Å). The structure was determined by direct methods and all atomic parameters including those for H atoms were refined by the full-matrix least-squares method. The final R-value was 0.053 (R_w = 0.0693).‡

Moffatt oxidation of each of the alcohols (**8a**) and (**8b**) gave the same ketone (**10**) [ν_{max} ($CHCl_3$) 1780 and 1750 cm^{-1}]. Tosylation of the epimeric mixture of (**8a**) and (**8b**) (*p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C, 24 h) gave the readily separable (chromatography on silica gel) toluene-*p*-sulphonates (**9a**) and (**9b**) in 62 and 19% yield, respectively. Displacement of the 7α-toluene-*p*-sulphonate (**9a**) with azide ion (NaN_3, dimethylformamide, 25 °C, 14 h) cleanly inverted the stereochemistry at C(7), affording a single azide (**11**) [m.p. 74—75 °C, ν_{max} ($CHCl_3$) 2110, 1755, and 1720 cm^{-1}]. Hydrogenation (H_2, 1 atm, 10% Pd–C, MeOH, 6 h) followed by acylation of the crude amine ($PhOCH_2COCl$, pyridine, CH_2Cl_2, 0 °C, 30 min) gave methyl (2*R**,5*R**,7*S**)-7-phenoxyacetamido-8-oxo-1-azabicyclo[3.3.0]octane-2-carboxylate (**1a**) as a colourless oil [ν_{max} ($CHCl_3$) 3320, 1750, 1720, and 1685 cm^{-1}] in 81% overall yield from the azide (**11**). Deprotection of the methyl ester was achieved by saponification (K_2CO_3, MeOH, H_2O) to give the potassium salt (**1b**), ^{1}H n.m.r. (D_2O) 1.26—2.56 [6H, m, $-CH_2CH(N)CH_2CH_2-$], 3.77—3.87 [1H, m, $-CH_2CH(N)CH_2-$], 4.05 (1H, t, J 8.4 Hz, $CH_2CHCO_2K^+$), 4.49 (2H, s, $PhOCH_2CO$), 4.80 [1H, dd, J 8.4 and J 11.6 Hz, C(O)NHCHC(O)N], and 6.84—7.25 (5H, m, Ph) in 74% yield.

The γ-lactam analogue (**2**) of penicillanic acid was obtained directly from benzyl 6-oxopenicillinate[6] (**12**) *via* a novel ring expansion, which we believe to be the first§ example of a C(6)–C(7) rearrangement of the β-lactam nucleus. Thus, treatment of the 6-oxopenicillinate (**12**) with excess of diazomethane (Et_2O, 0 °C, 4 h, then 25 °C, 14 h) gave benzyl

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

§ *Added in proof:* during the preparation of this communication a C(6)–C(7) rearrangement of the β-lactam of a spiropenicillinate[7] was reported.



Scheme 2

(2*R*,5*R*)-3,3-dimethyl-6-methoxy-8-oxo-1-aza-4-thiabicyclo-[3.3.0]oct-6-ene-2-carboxylate (**13**) [^{1}H n.m.r. δ ($CDCl_3$) 1.40 (3H, s, $-CH_3$), 1.46 (3H, s, $-CH_3$), 3.87 (3H, s, $-OCH_3$), 4.76 (1H, s, $-CHCO_2CH_2Ph$), 5.05 (1H, s, –NCHS–), 5.20 (1H, d, J_{AB} 12 Hz, H_A of $-OCH_2Ph$), 5.23 (1H, d, J_{AB} 12 Hz, H_B of $-OCH_2Ph$), 5.74 (1H, s, $-HC$=C–), 7.39—7.40 (5H, m, Ph), λ_{max} (MeOH) 208 nm (ε 32000)] in 50% yield after chromatography (Scheme 2). Saponification of this ester (NaOH, H_2O, dioxan, 25 °C, 1 h) followed by acidification and crystallisation from ethyl acetate, gave the free acid (**2**) (m.p. 188—189 °C) in 52% yield.

Both analogues (**1**) and (**2**) were tested for antibiotic activity (*Bacillus subtilis* ATCC 6633, and *Escherichia coli* super sensitive strain No. 21/30) and β-lactamase inhibition (*Bacillus cereus* β-lactamase II and *Klebsiella aerogenes* BRL 1003) and were shown to be inactive.

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